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(54) Title: A METHOD FOR PRODUCING A HYDROPHILIC COATING ON A SURFACE AND A MEDICAL ARTICLE PRODUCED BY THE METHOD

(57) Abstract

A hydrophilic coating with improved retention of water on a surface, especially a surface of a medical device such as a urethra catheter, prepared by applying on to the surface in one or more process steps at least one solution of components that will combine to form the hydrophilic coating. During the final process step, the surface is coated with an osmolality promoting agent, which is dissolved or emulgated in the solution or in the last solution to be applied, forming the hydrophilic coating.

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A METHOD FOR PRODUCING A HYDROPHILIC COATING ON A SURFACE AND A MEDICAL ARTICLE PRODUCED BY THE METHOD

This invention relates to a method of preparing a hydrophilic coating as described in the introductory part of claim 1.

It is known to coat medical devices, e.g., catheters for introduction into human cavities such as blood vessels, digestive organs and the urinary system, with a hydrophilic coating, as a minimum applied on that part of the surface which gets into contact with the mucous membranes, etc., during introduction of the device. Whereas such coating in dry condition is not particularly smooth, so that the handling of the device does not become inconvenient, when it is moistened with water immediately before introduction into the human body it becomes extremely slippery, thereby providing a substantially painless introduction.

A large number of methods are known for the production of hydrophilic surface coatings.

These methods are mainly based on the fact that the substrate to be provided with a hydrophilic surface coating, in the course of one or more process stages with intermediary drying and curing, is coated with one or more (mostly two) layers, which are caused to react with one another in different ways, e.g., by polymerization initiated by irradiation, by graft polymerization, by the formation of interpolymeric network structures, or by direct chemical reactions. Regarding this subject, please refer to DK-A-900 855, DK-B-159 018, EP-A-379 156, EP-A-454 293, EP-B2-93 093, GB-A-1 600 963, US-A-4 119 094, US-A-4 373 009, US-A-4 729 914, US-A-5 041 100, and US-A-5 120 816, and to WO-A-9005162 and WO-A-9119756.

According to a method known from US-A-5 001 009, a hydrophilic surface coating is prepared on a substrate by applying, in two stages or in one combined stage, on the substrate a reactive or an adhesive primer layer and then the actual hydrophilic surface layer, which in this case

comprises polyvinylpyrrolidone [PVP] as the active constituent. By this method, there is no chemical reaction between the components of the two layers applied.

Where a device of said type, e.g., a catheter, is to remain inside the body only for a short period, there may be a risk that water will be extracted from the hydrophilic surface coating and into the body fluids in the surrounding mucous membranes etc., owing to the higher osmotic potential of said body fluids. As a result of the extraction of water, the hydrophilic surface coating will have a tendency to stick to the surrounding tissues, and the removal of the medical device from the body may be painful.

EP-B-217 771 describes a method of said type for the production of an improved hydrophilic coating that maintains the smoothness of the coating for a longer period of time.

According to this method, on a hydrophilic coating prepared by an already known technique and cured in a separate process stage, an additional and separate coating is applied, consisting of a solution including an osmolality promoting agent and selected from among mono- and disaccharides, sugar alcohols, and nontoxic organic and inorganic salts, whereupon the solvent is allowed to evaporate. As a viscosity controlling agent the solution may also contain a polymer. When dried outside the human body a surface produced according to this method remains moist in a longer period of time than conventionally prepared hydrophilic surface coatings, and catheters with a hydrophilic coating improved in this way will be easier to remove than those with a conventional coating.

As distinct from said method, the method according to the present invention is characterized by the measures stated in the characterizing part of claim 1.

The method according to this invention leads to a simpler production and an improved stability as compared to the known method according to EP-B-217771, since the

osmolality promoting agent, without any use of an additional, separate coating step, is included in that solution from which the hydrophilic surface coating or its outermost layer is produced. The osmolality promoting agent is most frequently dissolved in the same solvent as the components for producing the hydrophilic coating, but may also merely be emulgated or suspended therein.

In the method of the invention the osmolality promoting agent may be any compound that ensures the desired equalization of the difference in osmotic pressures between the moistened coating and the surrounding body fluid. It may thus be selected from among osmolality increasing electrolytes, e.g., of the same kind as described in said EP-B-217771, namely mono- and disaccharides, sugar alcohols, and nontoxic organic or inorganic salts, which may be soluble or insoluble in the solution into which the agent is incorporated. In the method according to the invention, however, the osmolality promoting agent is preferably selected from among urea, amino acids, organic and inorganic acids, and polypeptides and/or mixtures hereof, said agent being preferably incorporated into the solution by dissolution or emulsification.

The term "urea" used herein should be understood to comprise urea that has been N-substituted or N,N-disubstituted by lower alkyl.

The preferred embodiment of the method according to the invention in principle relies on process stages corresponding to those described in said US-A-5 001 009, where a primer is first applied to the substrate, for instance a primer containing nitrocellulose applied in a solution. After drying of the primer layer, an outer layer is applied consisting of a solution of polyvinylpyrrolidone in a solvent selected from among tetrahydrofuran, methyl(ene) chloride, toluene, acetone, a lower aliphatic alcohol, cyclohexanone, C_2-C_4-alkyl acetates, butyrolactone, and dimethylformamide, the most important

constituent being ethyl alcohol. According to the invention, this solution contains urea as the osmolality promoting agent in a quantity of 1-20 per cent by weight, preferably 2-15 per cent by weight and particularly 3-8 per cent by weight on the basis of dry polyvinylpyrrolidone.

If said content of urea exceeds a value of about 10 per cent by weight, on the basis of dry polyvinylpyrrolidone, a smarting sensation may be felt at the introduction of the catheter, depending on the nature of the hydrophilic coating.

As explained in the following, testing achieved good results with a urea quantity of 5-6 per cent by weight. It was found that a significantly lower amount of urea does not give the desired effect with regard to retention of the water used to moisten the coating before introduction of the device, whereas a significantly larger amount may cause inconveniences in the form of a smarting sensation during the introduction.

The invention also relates to a medical device for introduction into a body cavity, as described in the introductory part of claim 5.

Such devices may especially include catheters, wound drains, and certain surgical instruments. Regardless of the fact that the primary object of this invention is the production of improved catheters for introduction into the urethra in connection with the treatment of dysuria and the achievement of bladder control, the invention embraces all such devices intended for the introduction into and withdrawal from a body cavity, whether for human or veterinary use.

A medical device of said type is, according to the invention, characterized in the features stated in the characterizing part of claim 5.

The example below illustrates the preparation according to the invention of a hydrophilic coating on a catheter based on a polyvinyl chloride [PVC] substrate as well as a test of the coated catheters prepared this way

with different contents of urea as the osmolality promoting agent, illustrating the improved retention of water on such produced hydrophilic surfaces.

E X A M P L E

A catheter made of PVC was prepared according to a modification of the method described in Example 1 in US-A-5 001 009 and coated on part of its surface with a hydrophilic coating with improved water retention by first applying a primer layer by immersion into a mixture of 5.4 g of low-viscosity nitrocellulose, 2 g of dibutylphthalate, and 1.9 g of polyvinyl butyral [PVB], in a mixed solvent comprising isopropanol, ethyl acetate, ethanol, and acetone (36:13:6:25:18:1.5 vol/vol). After drying for 5 minutes at 65°C, the catheter coated as described above was provided with an outer layer by immersion into a solution of 6.6 g of polyvinylpyrrolidone and 5 per cent by weight of urea in relation to polyvinylpyrrolidone in a solvent mixture of ethanol, ethyl acetate, and dimethylformamide (64:23.5:12.5). Finally, the catheter was dried at 65°C for 60 minutes.

Three healthy volunteers (A, B, and C) assessed the resistance when a catheter prepared according to said method was removed after a conventional catheterization, according to the following score system:

1 No resistance
2 Slight resistance
3 Great resistance

The table below shows the results:

T A B L E

Volunteer	Urea content, per cent by weight			
	6	4	3	0
A	1	1	3	3
B	1	1	1	1
C	1	2	3	3

PATENT CLAIMS

1. A method for the preparation of a hydrophilic coating with improved retention of water on a surface, wherein the surface, in one or more process steps, is coated with at least one solution of agents, which agents will combine to form such a hydrophilic coating, and wherein in the final process step an osmolality promoting agent is applied to the surface, characterized in that the osmolality promoting agent is incorporated into said solution or into the last solution applied of several such solutions and applied in the same process step as this solution.

2. A method according to claim 1, characterized in that the osmolality promoting agent is selected from among osmolality increasing electro-lytes.

3. A method according to claim 1, characterized in that the osmolality promoting agent is selected from among urea, amino acids, organic and inorganic acids, and polypeptides and mixtures thereof, and incorporated into said solution by dissolution or emulsification therein.

4. A method according to claim 3, where said solution comprises polyvinylpyrrolidone or a derivative thereof as the active component, characterized in that the osmolality promoting agent in the solution comprises urea in a quantity of 1-20 per cent by weight, preferably 2-15 per cent by weight and particularly 3-8 per cent by weight, based on the quantity of dry polyvinyl-pyrrolidone.

5. A medical device for introduction into a body cavity, which device on at least part of its surface has a hydrophilic coating, of which the water retention has been improved by means of an osmolality promoting agent, characterized in that said osmolality promoting agent is incorporated into the hydrophilic coating itself by incorporating the agent in a solution or

in the last solution applied from which the coating is formed.

6. A device according to claim 5, c h a r a c t e r i z e d in that the osmolality promoting agent has been selected from among osmolality increasing electrolytes.

7. A device according to claim 5, c h a r a c t e r i z e d in that the osmolality promoting agent has been selected from among urea, amino acids and polypeptides and mixtures thereof.

8. A device according to claim 5 or 6, where the layer(s) of the coating include(s) polyvinylpyrrolidone or derivatives thereof, c h a r a c t e r i z e d in that the osmolality promoting agent comprises urea in a quantity of 1-20 per cent by weight, preferably 2-15 per cent by weight and particularly 3-8 per cent by weight, based on the quantity of dry polyvinylpyrrolidone in the outermost layer.

9. A device according to any one of the claims 5-8, c h a r a c t e r i z e d in that the medical device is a catheter, mainly intended for introduction into the urethra.

INTERNATIONAL SEARCH REPORT

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PCT/DK 94/00035

A. CLASSIFICATION OF SUBJECT MATTER

IPC : A61L 29/00, C08J 7/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC : A61L, C08J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, WPI CLAIMS, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DK, A, 9200768 (UNO PLAST A/S), 11 December 1993 (11.12.93)	1-3,5-6,9
	&	
	EP, A1, 0586324 (UNO PLAST A/S), 9 March 1994 (09.03.94)	
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X	EP, A1, 0217771 (ASTRA MEDITEC AB), 8 April 1987 (08.04.87)	1-3,5-6,9
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A	EP, A1, 0093093 (ASTRA MEDITEC AB), 2 November 1983 (02.11.83)	1-9
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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